REMARKS

Reconsideration of the restriction requirement and allowance of the above-captioned patent application are respectfully requested. This application relates to aminoalkylphosphonates and related compounds as edg receptor agonists.

Claims 1 to 20 are currently pending in the application. Claims 1 (in part), 2 (in part), 3 and 4 to 20 (in part) have been withdrawn from consideration as drawn to non-elected subject matter. Claims 1, 2 and 4 to 6 have been rejected under 35 U.S.C. 103(a) as obvious over U.S. Patent No. 6,670,399 (Green). Claims 7 to 19 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. No claim has been allowed.

This amendment amends Claim 1 and cancels Claims 7 to 19. Upon entry of this Amendment, claims in the application will be Claims 1 to 6 and 20.

Enablement

All rejections pertaining to Claims 7 to 19 are rendered moot by the cancellation of these claims. The cancellation of these claims was made for purposes of advancing prosecution of the present application. Applicants reserve the right to prosecute the canceled subject matter in a future divisional application.

Restriction

The Examiner has required restriction of Claims 1 to 20 and an election of one of the following patentably distinct inventions (non-exhaustive):

Group I: Claims 1, 2 and 4 to 20 drawn to compounds of Formula (II), wherein **A** is PO_3H_2; **X** is a bond; R^1, R^2, R^3, R^4 and R^9 are hydrogen, m is 1 and p is 9; and methods of using the compound of Formula (II) to treat an immunoregulatory abnormaility, wherein the immunoregulatory abnormality is organ transplant rejection.

Group II: Claims 1, 2 and 4 to 20 drawn to compounds of Formula (II), wherein **A** is PO_3H_2; **X** is a O; R^1, R^2, R^3, R^4 and R^9 are hydrogen, m is 1 and p is 9; and

methods of using the compound of Formula (II) to treat an immunoregulatory abnormaility, wherein the immunoregulatory abnormality is bone marrow rejection.

Group III: Claims 1, 2 and 4 to 20 drawn to compounds of Formula (II), wherein **A** is PO_3H_2; **X** is O; R^1, R^2, R^3, R^4 and R^9 are hydrogen, m is 1 and p is 9; and methods of using the compound of Formula (II) to treat an immunoregulatory abnormaility, wherein the immunoregulatory abnormality is graft-versus-host disease.

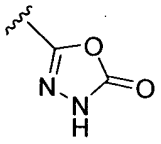
Group IV: Claims 1 to 20 drawn to compounds of Formula (II), wherein **A** is $-CO_2H$; **X** is O; R^1, R^2, R^3, R^4 and R^9 are hydrogen, m is 1 and p is 9; and methods of using the compound of Formula (II) to treat an immunoregulatory abnormaility, wherein the immunoregulatory abnormality is organ transplant rejection.

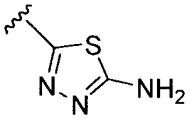
Group V: Claims 1 to 20 drawn to compounds of Formula (II), wherein **A** is $-SO_3H$; **X** is O; R^1, R^2, R^3, R^4 and R^9 are hydrogen, m is 1 and p is 9; and methods of using the compound of Formula (II) to treat an immunoregulatory abnormaility, wherein the immunoregulatory abnormality is organ transplant rejection.

Group VI: Claims 1 to 20 drawn to compounds of Formula (II), wherein **A** is $-PO(R^8)OH$; **X** is O; R^1, R^2, R^3, R^4 and R^9 are hydrogen, m is 1 and p is 9; and methods of using the compound of Formula (II) to treat an immunoregulatory abnormaility, wherein the immunoregulatory abnormality is organ transplant rejection.

Group VII: Claims 1 to 20 drawn to compounds of Formula (II), wherein **A** is 1H-tetrazolyl; **X** is O; R^1, R^2, R^3, R^4 and R^9 are hydrogen, m is 1 and p is 9; and methods of using the compound of Formula (II) to treat an immunoregulatory abnormaility, wherein the immunoregulatory abnormality is organ transplant rejection.

Group VIII: Claims 1 to 20 drawn to compounds of Formula (II), wherein **A** is 3-hydroxyisoxazolyl; **X** is O; R^1, R^2, R^3, R^4 and R^9 are hydrogen, m is 1 and p is 9; and methods of using the compound of Formula (II) to treat an immunoregulatory abnormaility, wherein the immunoregulatory abnormality is organ transplant rejection.

Group IX: Claims 1 to 20 drawn to compounds of Formula (II), wherein **A** is  ; **X** is O; R^1, R^2, R^3, R^4 and R^9 are hydrogen, m is 1 and p is 9; and methods of using the compound of Formula (II) to treat an immunoregulatory abnormaility, wherein the immunoregulatory abnormality is organ transplant rejection.

Group X: Claims 1 to 20 drawn to compounds of Formula (II), wherein **A** is  ; **X** is O; R^1, R^2, R^3, R^4 and R^9 are hydrogen, m is 1 and p is 9; and methods of using the compound of Formula (II) to treat an immunoregulatory abnormaility, wherein the immunoregulatory abnormality is organ transplant rejection.

Group I was elected with traverse during a telephone conversation with the Examiner. Applicants hereby confirm this election with traverse, except Applicants believe there is an error in Group I such that m should be 2 when **X** is a bond. *See* the compounds listed in Claim 6.

Applicants respectfully request reconsideration of the restriction requirement with respect to Claims 1 to 6 and 20 as amended and submit that these claims satisfy the unity of invention requirement because the groups are properly linked to form a single general inventive concept. As outlined in M.P.E.P. § 1893.03(d), a group of inventions is considered linked to form a single general inventive concept when there is a technical relationship among the

inventions that involves at least one common or corresponding special technical feature. The expression "special technical feature" is defined as meaning those technical features that define the contribution which each claimed invention, considered as a whole, makes over the prior art. In the instant claims, the special technical feature is the novel and non-obvious core structure embodied in Formula II. All compounds share this significant common chemical structure. The claimed compounds also possess the same utility as edg receptor agonists and for treating diseases or conditions mediated by that receptor. As such, unity of invention is present.

Applicants note that each group outlined by the Examiner is drawn to a specific species. **Thus, it appears that the Examiner has taken the position that each individual species within the genus of Formula II is a different invention for purposes of the unity of invention standard.** Applicants respectfully submit that this is incorrect.

Applicants have amended Claim 1 such that the claims are limited to a two atom linker between the acidic group **A** and the carbon attached to the amino group. On the other side of this carbon bearing the amino group is a 10 to 21-membered alkyl chain. Applicants submit that this structural formula defines an invention that makes a contribution over the prior art and thus satisfies the unity of invention standard.

The Examiner states that the "variables off the amine vary from compound to compound in the instant claims and when taken as a whole result in vastly different compounds." The Examiner further states that "the vastness of the claimed subject matter, and the complication in understanding the subject matter imposes a serious burden on any examination of the claimed subject matter." Applicants submit that these arguments are inapposite to a unity of invention determination. The standard for unity of invention is whether the group of inventions is considered linked to form a single general inventive concept such that there is a technical relationship among the inventions that involves at least one common or corresponding special technical feature meaning those technical features that define the contribution which each claimed invention, considered as a whole, makes over the prior art. The Examiner has failed to meet her burden of showing how the group of inventions are not linked to form a general inventive concept and how the group of inventions do not make a contribution over the prior art.

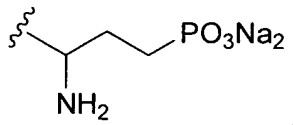
Based on the foregoing, Applicants submit that the restriction requirement is improper and respectfully request it be withdrawn. Applicants also respectfully request that the withdrawal of Claim 3 from consideration be reversed.

Obviousness

Applicants respectfully request reconsideration of the obviousness rejection of Claims 1, 2 and 4 to 6 over U.S. No. 6,670,399 (Green). As stated in M.P.E.P § 2142, in order to establish a prima facie case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. The burden is on the Examiner to provide some suggestion of the desirability of doing what the inventor has done.

Furthermore, M.P.E.P. § 2143.01 states that: "Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art."

Here, the closest compounds structurally are found in columns 37 to 40 of Green. These compounds consist of an alkyl chain varying from 1 to 5 carbons attached to a group having the following structure:



The Examiner alleges the following:

> The difference between the prior art of Green and the instant claims is that in the prior art the length of the alkyl chain differ. The length of the alkyl chain is longer in the instant application, i.e. wherein p is 9 to 20.

The Examiner further states the following:

Guided by the teaching of Green one skilled in the art would be able to make similar compounds by varying the length of the alkyl chain. The motivation would be to prepare similar compounds that are pharmacologically active.

Applicants respectfully disagree with the Examiner's rationale. There is no motivation, teaching or suggestion in Green that would lead one skilled in the art to modify the compounds of Green to arrive at the claimed compounds. **Applicants note that the difference here is changing the length of the alkyl chain from 1 to 5 carbon atoms to 10 to 21 carbon atoms.** This is a significant structural change that would no way have been obvious. As the chemical arts are unpredictable, such major differences in the structure could lead to significant changes in activity. Thus, one skilled in the art would have no motivation to significantly lengthen the alkyl chain and no reasonable expectation that such a change would result in compounds retaining their activity as Aß40 inhibitors.

The Examiner refers to the definition of "alkyl" at column 17, lines 61-63 of Green and asserts that the preferred embodiments of Green teach a straight chain alkyl with 30 or fewer atoms in it backbone. Applicants submit that it is improper to apply this definition to the compounds at columns 37 to 40 of Green. **Applicants could not identify a generic formula described in Green covering these compounds and teaching "alkyl" generally at this position.** In fact, the closest generic formula at column 14 teaches that R^3 is lower alkyl, defined as 1 to 6 carbon atoms, which teaches away from the claimed invention. Thus, Green does not in any way teach or suggest varying the alkyl chain at this position to up to 30 atoms and in fact teaches away from such long chain alkyl substitutions.

Applicants submit that the length of the alkyl chain having 10 to 21 carbon atoms is an important structural feature for the claimed compounds imparting agonist activity for the compounds on the edg 1 receptor. Based on the foregoing, Applicants respectfully request that the obviousness rejection be withdrawn.

Applicants respectfully request reconsideration and withdrawal of the requirement for restriction and obviousness rejection. Applicants submit that the application is in condition for allowance and passage thereto is earnestly requested. Any additional fees required in connection with this Response may be taken from Merck Deposit Account No. 13-2755. The Examiner is invited to contact the undersigned attorney at the telephone number provided below if such would advance the prosecution of the case.

Respectfully submitted,

By _____

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